The Action of Δ^2-Oxazolin-5-ones on 1,3,4-Oxadiazolium Salts

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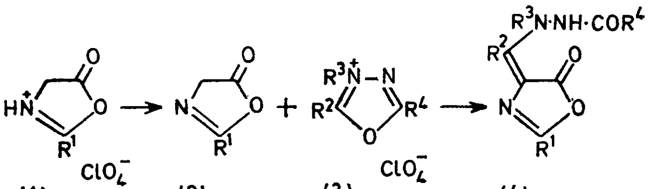
1,3,4-Oxadiazolium salts react with 2-methyl- and 2-phenyl-Δ^2-oxazolin-5-one to give *N'*-acylhydrazinomethylene-Δ^2-oxazolin-5-ones (4), which are converted into 1,5-disubstituted 4-acylamino-3-hydroxypyrazoles (5) on treatment with acid or alkali. Heating 4-[1-(*N'*-benzoyl-*N*-phenylhydrazino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (4a) with alkylamines yields 4-[1-(alkylamino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-ones (8).

1,3,4-OXADIAZOLIUM salts react with suitably constituted carbanions to form derivatives of pyrazole by a process involving successive electrophilic and nucleophilic attacks.[1] Since Δ^2-oxazolin-5-ones (saturated azlactones) readily react with electrophiles at the 4-position, with substitution, and with nucleophiles at the 5-position with ring-opening,[2] they appeared to be attractive substrates and we have accordingly studied their behaviour towards several 1,3,4-oxadiazolium salts.

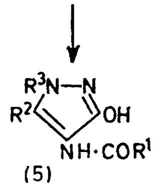
Treatment of 2-phenyloxazolinone (2a), generated from its hydroperchlorate[3] (1a) by the action of triethylamine, with 2-methyl-3,5-diphenyloxadiazolium perchlorate (3a) gave a yellow product (4a), whose colour and i.r. spectrum [$\nu_{max.}$ 1780 (C=O) cm^{-1}] indicated that the oxazolinone ring had remained intact; the presence of secondary amide absorptions showed that the oxadiazole ring had opened. The same compound was obtained in higher yield by adding an excess of triethylamine to a mixture of oxazolinium and oxadiazolium perchlorates. This procedure was followed in all subsequent preparations. Analogous acylhydrazinomethyleneoxazolinones (4b) and (4c) were obtained from the perchlorate (1a) and the oxadiazolium salts (3b) and (3c), respectively; reaction of the 2-methyl-5-oxo-oxazolinium perchlorate (1e) with the oxadiazolium salt (3b) similarly gave compound (4e). Addition of triethylamine to a mixture of the salt (1a) and 2,3-dimethyl-5-phenyloxadiazolium perchlorate (3d) yielded a crude oxazolinone (4d), which was shown by t.l.c. to be contaminated with the hydrazinopyrazole (6a), the product[4] of the action of base on the oxadiazolium salt. Similarly, a mixture of oxazolinone (4f) and pyrazole (6b) was formed from the salts (1e) and (3a); in this case, however, the hydrazinopyrazole was isolated after treatment of the mixture with alkali.

The yellow oxazolinones (4a—f) dissolved in alkali to give red solutions containing, presumably, the corresponding anions. Immediate acidification of an alkaline solution of compound (4b) regenerated the oxazolinone; but when the alkaline solutions were kept for several hours the colour was gradually discharged and acidification then precipitated the acylaminohydroxypyrazoles (5a—f).† The same rearrangement and deacylation occurred when the oxazolinones were heated with hydrochloric acid. The structures of the pyrazoles were established on the basis of spectral and analytical data; compound (5f) also had been prepared previously.[5]



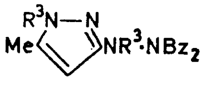
(1) (2) (3) (4)

	R¹	R²	R³	R⁴
a;	Ph	Me	Ph	Ph
b;	Ph	Ph	Ph	Me
c;	Ph	Et	Ph	Ph
d;	Ph	Me	Me	Ph
e;	Me	Ph	Ph	Me
f;	Me	Me	Ph	Ph



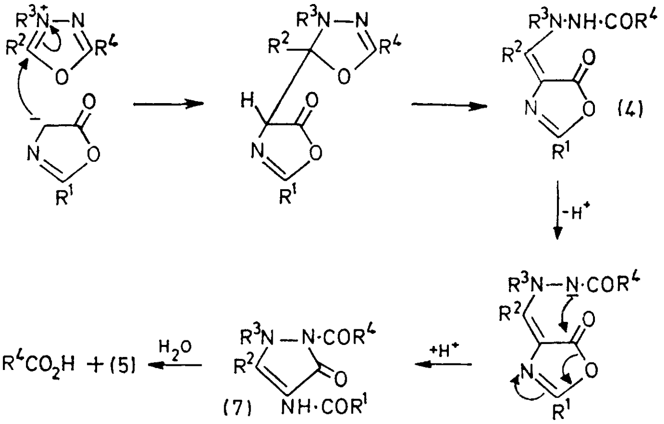
(5)

a; R^3 = Me
b; R^3 = Ph



(6)

The formation of the oxazolinones (4) and their conversion into the hydroxypyrazoles (5) (see Scheme) is an elaboration of the reaction of 1,3,4-oxadiazolium salts with ethyl cyanoacetate, β-diketones, and related compounds[1] in which, however, intermediates corresponding to the hydrazines (4) can rarely be isolated.



SCHEME

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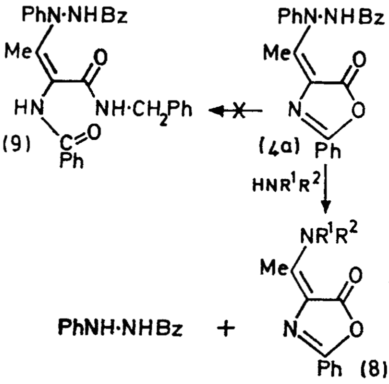
† These compounds are formulated as hydroxypyrazoles rather than pyrazolinones. The i.r. spectra of the solids show broad OH absorptions but the presence of minor amounts of pyrazolinone tautomers is not excluded (*cf.* A. R. Katritzky and F. W. Maine, *Tetrahedron*, 1964, **20**, 315).

[1] G. V. Boyd and S. R. Dando, *J. Chem. Soc.* (*C*), 1971, 225.
[2] W. Steglich, *Fortschr. chem. Forsch.*, 1969, **12**, 77.
[3] G. V. Boyd, *Chem. Comm.*, 1968, 1410.
[4] G. V. Boyd and S. R. Dando, *J. Chem. Soc.* (*C*), 1971, 2314.
[5] A. Michaelis, *Annalen*, 1906, **350**, 288.

A precedent for the rearrangement (4) ⟶ (7) is the formation of 4-benzamido-3-hydroxy-5-phenylpyrazole when 4-hydrazinomethylene-2-phenyl-Δ^2-oxazolin-5-one is heated;[6] the easy hydrolysis of *N′*-acylpyrazoles [(7) ⟶ (5)] has been observed before.[1]



a; $R^1 = PhCH_2$, $R^2 = H$
b; $R^1 = Bu$, $R^2 = H$
c; $R^1R^2 = C_4H_8$

Attempts to open the oxazolinone ring of compound (4a) without concomitant pyrazole formation failed: heating with benzylamine gave the (benzylamino-ethylidene)oxazolinone (8a) rather than the amide (9). Analogous compounds (8b) and (8c) were obtained with butylamine and pyrrolidine, respectively; no reaction occurred when aniline was used.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus, n.m.r. spectra were recorded at 60 MHz with a Perkin-Elmer R10 instrument, and i.r. spectra refer to Nujol mulls. The preparation of 1,3,4-oxadiazolium salts has been described.[7]

4-[1-(N′-*Benzoyl*-N-*phenylhydrazino*)*ethylidene*]-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (4a).—2-Methyl-3,5-diphenyl-1,3,4-oxadiazolium perchlorate (3a) (6·8 g) was added to a solution of 2-phenyl-5-oxo-Δ^2-oxazolinium perchlorate[3] (1a) (5·2 g) and triethylamine (8·0 g) in acetonitrile (50 ml). The *product* (1·6 g, 20%) separated after a few min as yellow needles, m.p. 206—208° (from acetonitrile–ethanol), $\nu_{max.}$ 3280, 1780, 1710, 1695, and 1620 cm^{-1}, τ ($CDCl_3$) 0·04br (NH), 2·05—2·90 (m, 3Ph), and 7·58 (s, Me) (Found: C, 72·8; H, 4·8; N, 10·4. $C_{24}H_{19}N_3O_3$ requires C, 72·6; H, 4·85; N, 10·6%). The same compound was obtained (17·6 g, 53%) when a suspension of the oxadiazolium salt (28·0 g) and the perchlorate (1a) (22·0 g) in acetonitrile (100 ml) was treated with triethylamine (28·0 g).

4-[α-(N′-*Acetyl*-N-*phenylhydrazino*)*benzylidene*]-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (4b).—Triethylamine (6·0 g) was added to a mixture of 5-methyl-2,3-diphenyl-1,3,4-oxadiazolium perchlorate (3b) (6·8 g), the oxazolinium perchlorate (1a) (5·2 g), and acetonitrile (50 ml). The resulting red solution was kept overnight; removal of the solvent left the yellow *oxazolinone* (3·8 g, 48%), m.p. 216—219° (from acetonitrile–ethanol), $\nu_{max.}$ 3180, 1780, 1745, 1672, 1625, and 1597 cm^{-1} (Found: C, 72·8; H, 4·95; N, 10·5. $C_{24}H_{19}N_3O_3$ requires C, 72·6; H, 4·85; N, 10·6%). Dissolution of this compound (1·0 g) in a mixture of 2N-sodium hydroxide (10 ml) and ethanol (10 ml) caused a red colouration; immediate acidification with N-hydrochloric acid regenerated the oxazolinone (0·8 g), identified by mixed m.p. and i.r. spectrum.

4-[1-(N′-*Benzoyl*-N-*phenylhydrazino*)*propylidene*]-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (4c).—This compound (1·8 g, 22%) was precipitated when the solution obtained from triethylamine (6·0 g), 2-ethyl-3,5-diphenyl-1,3,4-oxadiazolium perchlorate (3c) (7·0 g), the perchlorate (1a) (5·2 g), and acetonitrile (50 ml) was left at 0° overnight; yellow needles, m.p. 191—193·5° (from ethanol), $\nu_{max.}$ 3260, 1780, 1740, 1628, and 1619 cm^{-1} (Found: C, 72·8; H, 5·2; N, 10·1. $C_{25}H_{21}N_3O_3$ requires C, 73·1; H, 5·15; N, 10·25%).

4-[α-(N′-*Acetyl*-N-*phenylhydrazino*)*benzylidene*]-2-*methyl*-Δ^2-*oxazolin*-5-*one* (4e).—Triethylamine (6·0 g) was added to a suspension of 5-methyl-2,3-diphenyl-1,3,4-oxadiazolium perchlorate (3b) (6·8 g) and 2-methyl-5-oxo-Δ^2-oxazolinium perchlorate[8] (1e) (4·0 g) in acetonitrile (50 ml). The resulting red solution was kept for 30 min and the solvent was removed. The oily residue was warmed with aqueous ethanol to give the yellow *oxazolinone* (2·0 g, 30%), m.p. 168—169° (from ethanol), $\nu_{max.}$ 3240, 1780, 1740, 1680, and 1643 cm^{-1} (Found: C, 67·8; H, 5·05; N, 12·4. $C_{19}H_{17}N_3O_3$ requires C, 68·1; H, 5·1; N, 12·55%).

A similar preparation with 2,3-dimethyl-5-phenyl-1,3,4-oxadiazolium perchlorate (3d) (2·75 g), 2-phenyl-5-oxo-Δ^2-oxazolinium perchlorate (1a) (2·6 g), acetonitrile (25 ml), and triethylamine (3·0 g) gave a crude yellow solid (1·7 g), m.p. 91—97°, whose i.r. spectrum (1780 cm^{-1}) was consistent with the presence of the required 4-[1-(*N′*-benzoyl-*N*-methylhydrazino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (4d); t.l.c. showed that it was a mixture of two components, one of which was 3-(*N′N′*-dibenzoyl-*N*-methylhydrazino-1,5-dimethylpyrazole (6a). All attempts at separation failed.

Addition of triethylamine (6·0 g) to a suspension of 2-methyl-5-oxo-Δ^2-oxazolinium perchlorate (1e) (4·0 g) and the oxadiazolium salt (3a) (6·8 g) similarly gave an intractable yellow solid (4·6 g), which was shown by i.r. spectroscopy and t.l.c. to be a mixture of 4-[1-(*N′*-benzoyl-*N*-phenylhydrazino)ethylidene]-2-methyl-Δ^2-oxazolin-5-one (4f) and 3-(*N′N′*-dibenzoyl-*N*-phenylhydrazino)-5-methyl-1-phenylpyrazole (6b).

Formation of 3-*Hydroxy*-3-*acylaminopyrazoles* (5).—A solution of the oxazolinone (4a) (1·0 g) in a mixture of 2N-sodium hydroxide (10 ml) and ethanol (10 ml) was kept overnight. Addition of hydrochloric acid gave 4-*benzamido*-3-*hydroxy*-5-*methyl*-1-*phenylpyrazole* (5a) (0·5 g, 68%), m.p. 230—231° (from ethanol), $\nu_{max.}$ 3290, 2600br, 1645, and 1600 cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 1·55—2·75 (m, 2Ph), and 7·68 (s, Me) (Found: C, 70·0; H, 5·3; N, 14·3. $C_{17}H_{15}N_3O_2$ requires C, 69·6; H, 5·15; N, 14·35%). The same pyrazole (0·5 g) was obtained when a solution of the oxazolinone (1·0 g) in ethanol (10 ml) was heated under reflux with 5N-hydrochloric acid (10 ml) for 3 h and then poured into water.

4-*Benzamido*-3-*hydroxy*-1,5-*diphenylpyrazole* (5b).—This compound (0·9 g, 100%) was similarly obtained by treatment of the oxazolinone (4b) (1·0 g) with aqueous ethanolic sodium hydroxide and in 56% yield by heating with hydrochloric acid; m.p. 245—246° (from ethanol), $\nu_{max.}$ 3280, 2700br, 1655, and 1598 cm^{-1} (Found: C, 74·4; H, 4·9; N, 11·9. $C_{22}H_{17}N_3O_2$ requires C, 74·4; H, 4·85; N, 11·8%).

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[6] J. W. Cornforth, in 'The Chemistry of Penicillin,' ed. H. T. Clarke, Princeton University Press, Princeton, 1949, p. 757.

[7] G. V. Boyd and S. R. Dando, *J. Chem. Soc.* (*C*), 1970, 1397.

[8] A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newberry, *J. Chem. Soc.* (*C*), 1971, 598.

Treatment of the oxazolinone (4c) (0·2 g) with alkali or acid gave 4-*benzamido*-5-*ethyl*-3-*hydroxy*-1-*phenylpyrazole* (5c) (0·05 g, 33·5%), m.p. 239·5—240·5° (from ethanol), $\nu_{max.}$ 3360, 2600br, 1655, and 1600 cm^{-1} (Found: C, 70·1; H, 5·7; N, 13·6. $C_{18}H_{17}N_3O_2$ requires C, 70·4; H, 5·6; N, 13·7%).

A red solution resulted when the oxazolinone (4e) (0·5 g) was added to 2N-sodium hydroxide (10 ml) and ethanol (10 ml). By the following day the colour had faded. Neutralisation with hydrochloric acid followed by removal of the solvents left a solid which was extracted with chloroform. Evaporation of the extract gave 4-*acetamido*-3-*hydroxy*-1,5-*diphenylpyrazole* (5e) (0·2 g, 46%), m.p. 211—213° (from ethanol), $\nu_{max.}$ 3240, 3000br, 1660, 1610, and 1598 cm^{-1} (Found: C, 69·9; H, 5·2; N, 14·3. $C_{17}H_{15}N_3O_2$ requires C, 69·6; H, 5·15; N, 14·35%).

4-*Benzamido*-3-*hydroxy*-1,5-*dimethylpyrazole* (5d).—Treatment of the crude oxazolinone (4d) (0·5 g) with alkali gave the *pyrazole* (0·1 g), m.p. 227—228·5° (from ethanol), $\nu_{max.}$ 3280, 2600br, and 1645 cm^{-1} (Found: C, 62·4; H, 5·8; N, 18·6. $C_{12}H_{13}N_3O_2$ requires C, 62·4; H, 5·7; N, 18·2%).

The crude oxazolinone (4f) (1·0 g) was stirred with 2N-sodium hydroxide (10 ml) and ethanol (10 ml) for 30 min. The residual hydrazinopyrazole (6b) was filtered off and identified by direct comparison (mixed m.p. and i.r. spectrum) with an authentic specimen. The filtrate was kept overnight and neutralised with hydrochloric acid. The solvents were evaporated and the residue was extracted with chloroform. Evaporation left 4-acetamido-3-hydroxy-5-methyl-1-phenylpyrazole (5f) (0·1 g), m.p. 229—231° (from ethanol) (lit.,[5] 233°), $\nu_{max.}$ 3275, 2600br, 1660, 1620, and 1600 cm^{-1}.

Action of Amines on 4-[1-(N′-*Benzoyl*-N-*phenylhyrazino*)-*ethylidene*]-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (4a).—A mixture of the oxazolinone (1·0 g), benzylamine (1·1 g), and acetonitrile (10 ml) was heated under reflux for 10 h and then poured into water. The resulting oil solidified on trituration with ethanol to give 4-(1-*benzylaminoethylidene*)-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (8a) (0·6 g, 82%), m.p. 116—118·5° (from ethanol), $\nu_{max.}$ 3300, 1760, 1700, 1633, 1600, and 1589 cm^{-1}, τ ($CDCl_3$) 2·00—2·90 (m, 2Ph), 5·5 (d, CH_2), and 7·6 (s, Me) (Found: C, 74·1; H, 5·6; N, 9·5. $C_{18}H_{16}N_2O_2$ requires C, 73·95; H, 5·5; N, 9·6%).

4-(1-*Butylaminoethylidene*)-2-*phenyl*-Δ^2-*oxazolin*-5-*one* (8b) (0·6 g, 93%) was similarly prepared from the oxazolinone (4a) (1·0 g) and butylamine (0·73 g) in boiling acetonitrile (10 ml); m.p. 108·5—110·5° (from ethanol), $\nu_{max.}$ 3300, 1735, 1700, 1633, 1598, and 1584 cm^{-1}, τ ($CDCl_3$) 1·60br (NH), 2·00—2·80 (m, Ph), 6·62 (q) and 8·40 (m), and 9·00 (t, all Bu), and 7·58 (s, Me) (Found: C, 69·8; H, 7·2; N, 10·9. $C_{15}H_{18}N_2O_2$ requires C, 69·75; H, 7·0; N, 10·85%).

2-*Phenyl*-4-(1-*pyrrolidinoethylidene*)-Δ^2-*oxazolin*-5-*one* (8c) (0·6 g, 94%) was similarly obtained from pyrrolidine (0·71 g), and had m.p. 195° (from ethanol), $\nu_{max.}$ 1780, 1700, 1620, and 1598 cm^{-1} (Found: C, 70·7; H, 6·4; N, 11·0. $C_{15}H_{16}N_2O_2$ requires C, 70·4; H, 6·3; N, 10·95%). The oxazolinone was recovered after being boiled with aniline in acetonitrile for 10 h.

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